L Number	Hits	Search Text	DB	Time stamp
1	8777	poly$2e$5ene$2glycol$5	USPAT; US-PGPUB	2002/10/29 12:06
2	8802	poly$2e$5ene$2glycol$6	USPAT; US-PGPUB	2002/10/29 12:06
3	1743	peg$1{d4:5}	USPAT; US-PGPUB	2002/10/29 12:56
4	1445	pegylat$4	USPAT; US-PGPUB	2002/10/29 12:54
5	11588	poly$2e$5ene$2glycol$5 or poly$2e$5ene$2glycol$6 or peg$1{d4:5} or pegylat$4	USPAT; US-PGPUB	2002/10/29 12:55
6	64929	cytokine$1 or (growth adj factor$6) or hormone$1	USPAT; US-PGPUB	2002/10/29 12:56
7	163	(poly$2e$5ene$2glycol$5 or poly$2e$5ene$2glycol$6 or peg$1{d4:5} or pegylat$4) same (cytokine$1 or (growth adj factor$6) or hormone$1)	USPAT; US-PGPUB	2002/10/29 13:15
8	1	4179337.pn.	USPAT; US-PGPUB	2002/10/29 13:29
9	1	6183738.pn.	USPAT; US-PGPUB	2002/10/29 13:29
10	13355	(tum$2r adj necrosis) or tnf$7	USPAT; US-PGPUB	2002/10/29 13:30
11	48	((tum$2r adj necrosis) or tnf$7) same (poly$2e$5ene$2glycol$5 or poly$2e$5ene$2glycol$6 or peg$1{d4:5} or pegylat$4)	USPAT; US-PGPUB	2002/10/29 13:30

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     (FILE 'HOME' ENTERED AT 10:43:10 ON 29 OCT 2002)

     INDEX 'ADISALERTS, ADISINSIGHT, ADISNEWS, AGRICOLA, ANABSTR, AQUASCI,
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     CANCERLIT, CAPLUS, CEABA-VTB, CEN, CIN, CONFSCI, CROPB, CROPU, DDFB,
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              0*  FILE WPINDEX
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               E ADV DRUG ?/JT
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     FILE 'CAPLUS' ENTERED AT 10:50:02 ON 29 OCT 2002
L3         1058 S L2
L4            1 S L3 AND ZALIPSKY ?/AU

     FILE 'STNGUIDE' ENTERED AT 10:50:48 ON 29 OCT 2002

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               E AM ASS ?/JT
               E AMER ASS ?/JT

     FILE 'MEDLINE' ENTERED AT 10:59:04 ON 29 OCT 2002
               E POLYETHYLENE?/CT
               E POLYETHYLENEGLYCOL/CT
               E PEG/CT
               E E151+ALL
               E E158+ALL
L5         11897 S (POLYETHYLENE?(3A)GLYCOL) OR PEG
L6        574153 S CYTOKINE? OR (GROWTH FACTOR?) OR HORMON? OR GRANULOCYTE?
L7           642 S L5 AND L6
L8            86 S L5(5A)L6

     FILE 'STNGUIDE' ENTERED AT 11:05:53 ON 29 OCT 2002

     FILE 'MEDLINE' ENTERED AT 11:15:42 ON 29 OCT 2002

     FILE 'STNGUIDE' ENTERED AT 11:16:17 ON 29 OCT 2002
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L8 ANSWER 36 OF 86 MEDLINE
AU Wang L; Wu Y; Zhang Y
TI In vivo antitumor effects of polyethylene glycol--modified recombinant human interleukin-2 on mouse uterine cervical carcinoma.
SO CHUNG-HUA CHUNG LIU TSA CHIH [CHINESE JOURNAL OF ONCOLOGY], (1996 Jul) 18 (4) 253-5.
Journal code: 7910681. ISSN: 0253-3766.
AN 1998048559 MEDLINE
LA Chinese
AB Polyethylene glycol (PEG-8000) -modified recombinant human interleukin-2 (**PEG**-rIL-2) is a **cytokine** with prolonged circulatory half-life. In this paper, the antitumor effects of PEG-rIL-2 against mouse uterine cervical carcinoma (U14) transplanted intraperitoneally. . .

US-PAT-NO: 5605801

DOCUMENT-IDENTIFIER: US 5605801 A

TITLE: Methods of detecting lesions in the platelet-activating factor acetylhydrolase gene

---------- KWIC ---------

For pathological conditions of the lung, administration of PAF-AH by the pulmonary route is particularly indicated. Contemplated for use in pulmonary administration are a wide range of delivery devices including, for example, nebulizers, metered dose inhalers, and powder inhalers, which are standard in the art. Delivery of various promins to the lungs and circulatory system by inhalation of aerosol formulations has been described in Adjei et al., Pharm. Res., 7(6): 565-569 (1990) (leuprolide acetate); Braquet et al., J. Cardio. Pharm., 13(Supp. 5): s. 143-146 (1989) (endothelin-1); Hubbard et al., Annals of Internal Medicine, III(3), 206-212 (1989) (.alpha.1-antitrypsin); Smith et al., J. Clin. Invest., 84: 1145-1146 (1989) (.alpha.-1-proteinase inhibitor); Debs et al., J. Immunol., 140: 3482-3488 (1933) (recombinant gamma interferon and **tumor necrosis** factor alpha); Patent Cooperation Treaty (PCT) International Publication No. WO 94/20069 published Sep. 15, 1994 (recombinant **pegylated** granulocyte colony stimulating factor).

US-PAT-NO: 6217869

DOCUMENT-IDENTIFIER: US 6217869 B1

EFD 1994

TITLE: Pretargeting methods and compounds

---------- KWIC ---------

It is known that **PEGylation** may result in proteins and polypeptides having
reduced immunogenicity and altered serum clearance properties. It is further
known that PEG modified protectors are resistant to metabolic deactivation.
The following references are representative of PEG modification of proteins.
Wang et al., Cancer Res., 53, 4588-4597 (1993), who describe PEG attachment to
a chimeric toxin; Rosenberg et al., J. Biol. Chem., 267 (32), 2289-2293
(1992), who describe PEG modification of asialofetuin; Somack et al., Free Rad.
Res. Comms., 12-13, 553-562 (1991), who describe PEG modification of
superoxide dismutase; Malik et al., Exp. Hematol., 20, 1028-1035 (1992) who
describe PEG modification of macrophage colony stimulating factor (GM-CSF) to
produce derivatives having conserved biological activity; and Tsutsumi et al.,
Japan J. Cancer Res., 85, 9-12 (1994) who describe PEG modification of **tumor**
necrosis factor to produce conjugates having improved anti-tumor activity. In
some instances PEG modification of a protein has been disclosed to result in
loss of biological activity. (See, e.g., Wang et al., Id.; Sumack et al, Id.
and Tsutsumi et al., Id., in this regard). However, in most instances this can
be obviated or alleviated by optimizing the amount of bound glycol residues,
the particular means for their attachment, or by the use of protecting agents
which protect active sites, e.g., binding sites, during **PEGylation**.
Essentially, in the present invention, the particular ligand, anti-ligand,
targeting moiety or active agent will be derivatized with one or more glycol
residues, e.g., polyethylene glycol, and then assayed for activity. In the
case of the ligand or anti-ligand or targeting moiety this will be determined
in binding assays which assay the ability of the glycol derivatized moiety to

bind the corresponding anti-ligand or ligand.

US-PAT-NO: 5750503

DOCUMENT-IDENTIFIER: US 5750503 A

TITLE: Compositions of G-CSF and TNF-BP for prophylaxis and treatment of
septic shock

---------- KWIC ---------

TNF-BPs, their isolation from natural sources or their preparation by recombinant methods, including the preparation of specific constructs such as
chimaeric polypeptides comprising in addition to the TNF binding part an
immunoglobulin part, are described in the following patent publications: EP 308
378, EP 422 339, GB 2 218 101, EP 393 438, WO 90/13575, EP 398 327, EP 412 486,
WO 91/03553, EP 418 014, JP 127,800/1991, EP 433 900, U.S. Pat. No. 5,136,021, GB 2 246 569, EP 464 533, WO 92/01002, WO 92/13095, WO 92/16221, EP
512 528, EP 526 905, WO 93/07863, EP 568 928, WO 93/21946, WO 93/19777 and EP
417 563 and by Loetscher et al. (J. Biol. Chem. 266, 18324-18329, 1991; in
case of the purification of a chimaeric polypeptide comprising a part of IgG1
the protein G affinity purification step is replaced by a protein A affinity
purification step with which a man skilled in the art is familiar with).
Specifically preferred are TNF-BPs in the form of recombinant soluble parts of
the human TNFR, especially the p55-TNFR, which parts binds TNF, or chimaeric
polypeptides comprising such soluble parts and immunoglobulin parts as defined
above and as described in EP 417 563. The definition of TNF-BP of the present
invention includes TNF-BPs which have been modified chemically by means known
in the art and as described above for G-CSF, e.g., by linkage to a water
soluble polymer, e.g., polyethyleneglycol or polypropyleneglycol by methods
described in the state of the art, e.g., in WO 92/16221.

US-PAT-NO: 6399385

DOCUMENT-IDENTIFIER: US 6399385 B1

TITLE: Methods for rapid PEG-modification of viral vectors, compositions for enhanced gene transduction, compositions with enhanced physical stability, and uses therefor

---------- KWIC ---------

Francis et al., "**PEGylation of Cytokines** and Other Therapeutic Proteins and Peptides:the Importance of Biological Optimisation of Coupling Techniques". International Journal of Hematology, 68:1-18 (Jul. 1998).

US-PAT-NO: 6342369

DOCUMENT-IDENTIFIER: US 6342369 B1

TITLE: Apo-2-receptor

---------- KWIC ---------

The antibodies may optionally be covalently attached or conjugated to one or
more chemical groups. A polyol, for example, can be conjugated to an antibody
molecule at one or more amino acid residues, including lysine residues as
disclosed in WO 93/00109. Optionally, the polyol is a poly(alkelene glycol),
such as poly(ethylene glycol) (PEG), however, those skilled in the art
recognize that other polyols, such as, for example, poly(propylene glycol) and
polyethylene-polypropylene glycol copolymers, can be employed using techniques
for conjugating PEG to polypeptides. A variety of methods for **pegylating**
polypeptides have been described. See, e.g. U.S. Pat. No. 4,179,337 which
discloses the conjugation of a number of **hormones** and enzymes to PEG and
polypropylene glycol to produce physiologically active compositions having
reduced immunogenicities.

US-PAT-NO: 6306820

DOCUMENT-IDENTIFIER: US 6306820 B1

TITLE: Combination therapy using a TNF binding protein for treating TNF-mediated diseases

---------- KWIC ---------

There are a number of attachment methods available to those skilled in the art,
including acylation reactions or alkylation reactions (preferably to generate
an amino-terminal chemically modified protein) with a reactive water soluble
molecule. See, for example, EP 0 401 384; Malik et al. (1992), Exp. Hematol.,
20:1028-1035; Francis (1992), Focus on **Growth Factors,** 3(2):4-10, published by
Mediscript, Mountain Court, Friern Barnet Lane, London N20 OLD, UK; EP 0 154
316; EP 0 401 384; WO 92/16221; WO 95/34326; WO 95/13312; WO 96/11953; WO
96/19459 and WO 96/19459 and the other publications cited herein that relate to
pegylation, the disclosures of which are hereby incorporated by reference.

US-PAT-NO: 6048720

DOCUMENT-IDENTIFIER: US 6048720 A

TITLE: Conjugates of a polypeptide and a biocompatible polymer

---------- KWIC ---------

In WO 94/13322 (Farmitalia Carlo Erba) it is shown that **pegylation** can be carried out without impairing the function of certain sites essential for the function of the particular protein ("first substance"). This is achieved by protecting the sites by contacting the first substance with a second substance which specifically binds to the said sites. More particularly, the **pegylation** is carried out by immobilizing the particular protein on a resin with ligands having specific affinity to the said protein. Second substances are for instance complementary biological molecules. Examples of couples disclosed in WO 94/13322 are antibody (first substance)--corresponding antigen (second substance); specific inhibitor (first substance)--enzyme (second substance); **growth factor** (first substance)--corresponding receptor (second substance), or the reverse of each of these couples.

US-PAT-NO: 5849535

DOCUMENT-IDENTIFIER: US 5849535 A

TITLE: Human growth hormone variants

---------- KWIC ---------

Human growth **hormone** variants, DNA encoding the variants, vectors, host cells,
pegylated forms of the variants, as well as methods of making the variants are
disclosed.

This invention relates to certain growth **hormone** variants, and **pegylated** forms
thereof, for use as agonists or antagonists of human growth **hormone**.

FIG. 11 shows the effect of daily subcutaneous injections (0.25 mg/kg) of
various antagonist hGH variants of the present invention on insulin-like **growth**
factor-I (IGF-I) levels in Rhesus monkeys. Both **pegylated** and non-**pegylated**
forms of the variants were tested. See Example XIII.

A variety of methods for **pegylating** proteins have been described. See, e.g.,
U.S. Pat. No. 4,179,337 (issued to Davis et al.), disclosing the conjugation
of a number of **hormones** and enzymes to PEG and polypropylene glycol to produce
physiologically active non-immunogenic compositions. Generally, a PEG having
at least one terminal hydroxy group is reacted with a coupling agent to form an
activated PEG having a terminal reactive group. Id. This reactive group can
then react with the .alpha.- and .epsilon.-amines of proteins to form a
covalent bond. Conveniently, the other end of the PEG molecule can be
"blocked" with a non-reactive chemical group, such as a methoxy group, to
reduce the formation of PEG-crosslinked complexes of protein molecules.

The sites of **pegylation** of a protein are also somewhat constrained by the
reactivities of the various primary amines. For example, a potential lysine in
the Site 1 **hormone**-receptor binding interface of the B2036 variant (K41) is
relatively unreactive with M-SPA-PEG(5000). See Example X. Thus, moderately
pegylated B2036 variant preparations, having on the order of four to six PEGs

per variant molecule, retain the ability to bind hGH receptor at Site 1,
despite the presence of a potential **pegylation** site at this binding interface.

Furthermore, amino acid substitutions introducing or replacing lysines alter
the locations of potential **pegylation** sites. For example, in the B2036 variant, the K168A and the K172R substitutions reduce the number of sites
available for **pegylation at the hormone**-receptor Site 1 binding interface. The
replacement of G120 with a different amino acid disrupts hGH binding at Site 2,
converting the molecule to an hGH antagonist. The substitution of lysine for
glycine at this position provides an additional potential **pegylation** site in
Site 2, which is expected to impair any residual binding at this site. The
reactivities of the primary amines in the B2036 variant are shown in Example X.

The G120K substitution was added to generate a better antagonist candidate,
although other substitutions at that position are acceptable. Any amino acid
can be substituted at G120 to generate an antagonist; more preferably, the
substitution is lysine, arginine, tryptophan, tyrosine, phenylalanine, or
glutamate. The R64K substitution was omitted so as to protect site I binding
residues from **pegylation**. Similarly, the K168A and the K172R substitutions
were added to B2036 to reduce the number of sites available for **pegylation at the hormone**-receptor site I binding interface. In contrast, the G120K substitution makes available an additional lysine for **pegylation** while providing an effective site 2 block.

2. A method of producing a **pegylated** human growth **hormone** variant, comprising:

(a) **pegylating** the human growth **hormone** variant of claim 1;

(b) applying the **pegylated** human growth **hormone** variant to a cation exchange
chromatography column; and

(c) eluting the **pegylated** human growth **hormone** variant.

US-PAT-NO: 5641749

DOCUMENT-IDENTIFIER: US 5641749 A

TITLE: Method for treating retinal ganglion cell injury using glial cell
line-derived neurothrophic factor (GDNF) protein product

---------- KWIC ---------

Pegylation may be carried out by any of the pegylation reactions known in the
art. See, for example: Focus on Growth Factors, 3 (2):4-10, 1992; EP 0 154
316, the disclosure of which is hereby incorporated by reference; EP 0 401 384;
and the other publications cited herein that relate to pegylation. The
pegylation may be carried out via an acylation reaction or an alkylation
reaction with a reactive polyethylene glycol molecule (or an analogous reactive
water-soluble polymer).